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PYRIDINE-1-OXIDES. I. SYNTHESIS OF SOME NICOTINIC ACID DERIVATIVES[1]

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Although pyridine-1-oxide has been known for some time (1), it has not been until recent years that its versatility as an intermediate has been appreciated. As a result of these recent efforts, largely by Japanese workers (2) and by Hertog (3–9), it has been amply demonstrated that pyridine and pyridine derivatives containing the N-oxide grouping are highly reactive and useful compounds. The present paper reports improved syntheses of a number of important derivatives of nicotinic acid by utilization of the N-oxides of nicotinamide, nicotinic acid, and 3-picoline as synthetic intermediates.

Nicotinamide-1-oxide (I) has been prepared previously only by indirect methods. Jujo (10) prepared the compound by partial hydrolysis of nicotinonitrile-1-oxide, but his recorded melting point (275–276° dec.) indicates that his product was probably contaminated with some nicotinic acid-1-oxide. Shimizu (11) prepared I by ammonolysis of methyl nicotinate-1-oxide and recorded a melting point of 282–284° (dec.). We have now found that this compound (I) may be prepared directly from nicotinamide by the action of hydrogen peroxide in glacial acetic acid, the melting point of our product (291–293° dec.) being somewhat higher than previously reported. Nicotinamide-1-oxide (I) may also be prepared, although in lower yield, by oxidation and partial hydrolysis of nicotinonitrile with hydrogen peroxide in glacial acetic acid.

Treatment of nicotinamide-1-oxide (I) with a mixture of phosphorus pentachloride and phosphorus oxychloride gave 2-chloronicotinonitrile (II) in 52% yield. This synthesis represents a considerable improvement over previous methods for the preparation of II involving either the dehydration of 2-chloronicotinamide (III) (12) or the Sandmeyer reaction on 3-amino-2-chloropyridine (13). Treatment of 2-chloronicotinonitrile (II) with alcoholic ammonia at 150–177°, or with anhydrous ammonia at 130°, led to the hithertofore unknown 2-aminonicotinonitrile (V) in yields of 79% and 75% respectively. Alkaline hydrogen peroxide converted V into 2-aminonicotinamide (VI) in good yield,* thus providing a convenient synthesis of VI comparing favorably with previously described methods (14–16). Direct hydrolysis of V with concentrated hydrochloric acid gave 2-aminonicotinic acid (IV) in 94.5% yield. Hydrolysis of

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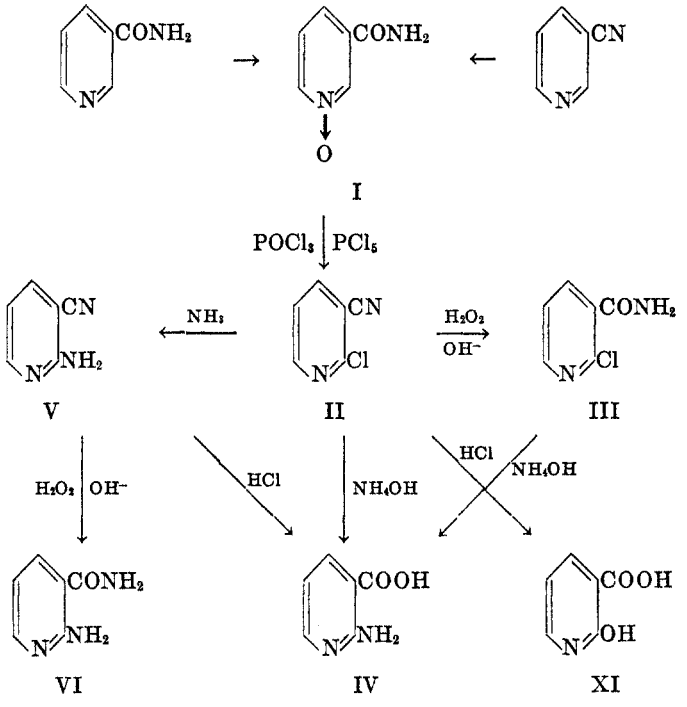
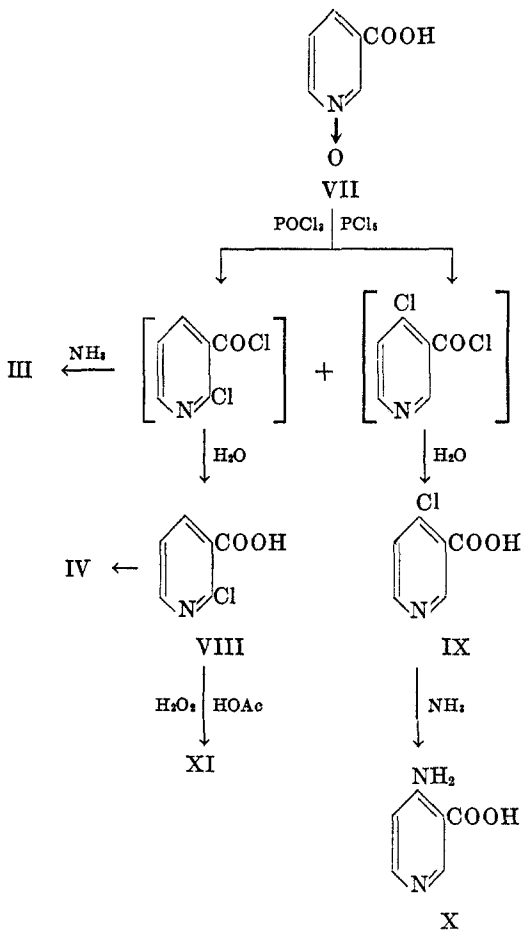
* *Note added in proof:* This conversion may be carried out somewhat more conveniently, although in reduced yield 66%, accompanied by an isolated 18% of 2-aminonicotinic acid) by heating 2-aminonicotinonitrile (1 g.) with concentrated ammonium hydroxide (10–15 ml.) at 105° for 12 hours in a sealed tube.

2-chloronicotinonitrile (II) with concentrated hydrochloric acid gave 2-hydroxynicotinic acid (XI) in 81% yield, while treatment with alkaline hydrogen peroxide yielded 2-chloronicotinamide (III) in 62% yield. It is noteworthy that no replacement of chlorine was observed when III was treated with alcoholic ammonia at elevated temperatures in a sealed tube, although under similar conditions 2-chloronicotinonitrile (II) was smoothly converted to V. However, the action of aqueous ammonia on II or III led to 2-aminonicotinic acid (IV), although in low yields.

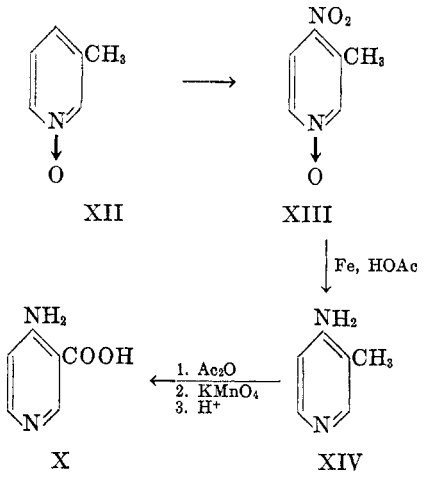


The action of hydrogen peroxide in glacial acetic acid on nicotinic acid gave nicotinic acid-1-oxide (VII) in good yield (17, 18). Treatment of VII with a mixture of phosphorus pentachloride and phosphorus oxychloride, followed by decomposition of the reaction mixture with water, gave 2-chloronicotinic acid (VIII) in 41% yield and 4-chloronicotinic acid (IX) in 5% yield. The structure of IX, previously unreported, was established by conversion to the known 4-aminonicotinic acid (X) with aqueous ammonia. 2-Chloronicotinic acid (VIII) has been prepared previously by permanganate oxidation of 2-chloro-3-picoline (obtained *via* 2-amino- and 2-hydroxy-3-picoline) (19) and by the action of phosphorus oxychloride and phosphorus pentachloride on 2-hydroxynicotinic acid [obtained from quinolinic acid *via* the anhydride (20–22) or imide (22, 23)]. In view of the convenient synthesis of 2-hydroxynicotinic acid developed above, the preferred route to 2-chloronicotinic acid may now be considered to be from nicotinamide *via* I, II, and XI.

Treatment of 2-chloronicotinic acid (VIII) with hydrogen peroxide in glacial acetic acid gave 2-hydroxynicotinic acid (XI) as the only isolable product, while ammonolysis with aqueous ammonia gave 2-aminonicotinic acid (IV), although only in 17 % yield. When the crude reaction mixture of nicotinic acid-1-oxide, phosphorus pentachloride, and phosphorus oxychloride was decomposed with benzene saturated with ammonia, 2-chloronicotinamide (III) was obtained in 35 % yield.



A convenient synthesis of 4-aminonicotinic acid (X) has been developed from 3-picoline-1-oxide (XII) (24). Nitration of XII gave 4-nitro-3-picoline-1-oxide (XIII) (25) in 76 % yield, and this compound was then reduced with iron and acetic acid to 4-amino-3-picoline (XIV). Acetylation of XIV followed by oxidation with dilute neutral potassium permanganate and hydrolysis gave 4-aminonicotinic acid (X). This synthesis of X from 3-picoline is considerably more convenient than the previously described 4-step synthesis from the relatively inaccessible cinchomeronic acid (26, 27).



EXPERIMENTAL[4]

Nicotinamide-1-oxide (I). *Method A*. A mixture of 5.0 g. (0.041 mole) of nicotinamide, 8 ml. (0.069 mole) of 30% hydrogen peroxide, and 50 ml. of glacial acetic acid was heated on a steam-bath for a period of four hours. It was then diluted with 100 ml. of water and evaporated to dryness under reduced pressure. The solid residue was dissolved in 20 ml. of boiling water, and the filtrate was diluted with 5 ml. of absolute ethanol. Cooling caused the separation of 4.4 g. (78%) of colorless crystals of nicotinamide-1-oxide, m.p. 291–293° (dec.).

Anal. Calc'd for $C_6H_6N_2O_2$: C, 52.2; H, 4.4; N, 20.3.
Found: C, 52.3; H, 4.3; N, 20.5.

Method B. A mixture of 5.0 g. of nicotinonitrile, 6.3 ml. of 30% hydrogen peroxide, and 15 ml. of glacial acetic acid was allowed to stand at room temperature for 24 hours and then worked up as described above. Recrystallization of the residue from aqueous ethanol gave 1.5 g. (22.6%) of nicotinamide-1-oxide, identical with that prepared by method A.

2-Chloronicotinonitrile (II). A mixture of 14 g. of nicotinamide-1-oxide, 29.7 g. of phosphorus pentachloride, and 40 ml. of phosphorus oxychloride was heated at 115–120° for a period of 1½ hours. The cooled reaction solution was concentrated under reduced pressure to a syrup which was added to ice. After standing overnight at 0°, the resulting light brown solid was removed by filtration, dried at 70° for two hours, and sublimed at 85–90°/0.5 mm. In this way there was obtained 6.9 g. (50%) of colorless crystals, m.p. 106–107°. By making the above filtrates alkaline and extracting with ether, an additional 0.5 g. of solid was obtained which gave 0.35 g. of 2-chloronicotinonitrile on sublimation; total yield, 7.25 g. (52%).

Anal. Calc'd for $C_6H_3ClN_2$: C, 52.0; H, 2.2; N, 20.2.
Found: C, 52.1; H, 2.2; N, 19.9.

2-Aminonicotinonitrile (V). A mixture of 2.0 g. of 2-chloronicotinonitrile and 60 ml. of absolute ethanol saturated with anhydrous ammonia was placed in a glass liner within a stainless-steel pressure bomb, which was then heated at 177° for six hours. The reaction mixture was evaporated to dryness, and the light brown residue washed with a small quantity of ice-water, dried, and sublimed at 90–100°/0.5 mm. Yield, 1.35 g. (79%), m.p. 131–133°.

2-Aminonicotinonitrile (V) was also obtained in 75% yield by heating 2-chloronicotino-

[4] All melting points are corrected. The microanalyses were performed by Mrs. Esther Fett, Mrs. Lucy Chang, and Mr. Joseph Nemeth. The authors are indebted to Mr. Edward Sutoris for help with some of the experimental work.

nitrile with an excess of liquid ammonia in a sealed tube at 130° for 1½ hours, and then working up the reaction mixture as described above.

Anal. Calc'd for $C_6H_5N_3$: C, 60.5; H, 4.2; N, 35.3.

Found: C, 60.3; H, 4.3; N, 35.0.

2-Aminonicotinamide (VI). To a mixture of 1.0 g. of 2-aminonicotinonitrile, 0.46 g. of solid potassium hydroxide, and 20 ml. of absolute ethanol contained in a 500-ml. flask fitted with an efficient stirrer was added slowly 20 ml. of 30% hydrogen peroxide. The reaction mixture then was heated at 60–70° with stirring for 30 minutes, an additional 5 ml. of 30% hydrogen peroxide was added, and heating and stirring were continued for 30 minutes. The reaction mixture was then transferred to a 50-ml. Erlenmeyer flask, the reaction flask washed out with 15 ml. of ethanol, and the washings were added to the reaction mixture. Chilling gave 0.67 g. of 2-aminonicotinamide, while concentration of the filtrate yielded an additional 0.21 g. for a total yield of 0.88 g. (76.5%), m.p. 199°. A mixture melting point determination with an authentic sample of 2-aminonicotinamide gave no depression.

Acidification of the above filtrates followed by chilling yielded 0.03 g. (2.6%) of 2-aminonicotinic acid, m.p. 310° (dec.).

2-Hydroxynicotinic acid (XI). *Method A.* A solution of 1.00 g. of 2-chloronicotinonitrile (II) in 5 ml. of concentrated hydrochloric acid was heated under reflux for five hours. The reaction mixture solidified immediately on cooling. Addition of 10 ml. of water followed by addition of concentrated ammonium hydroxide to *p*H 10 gave a clear solution which then was readjusted to *p*H 4–5 with hydrochloric acid. Cooling gave 0.71 g. of 2-hydroxynicotinic acid as white needles, m.p. 258–260°. Concentration of the filtrate gave an additional 0.11 g., total yield 81%. The product was identical with an authentic sample prepared from 2-aminonicotinic acid by the method of Philips (21) and also with a sample prepared from 2-chloronicotinic acid by Method *B* below.

Anal. Calc'd for $C_6H_5NO_3$: C, 51.8; H, 3.6; N, 10.1.

Found: C, 52.2; H, 3.5; N, 10.1.

Method B. A mixture of 2.0 g. of 2-chloronicotinic acid, 15 ml. of glacial acetic acid, and 2 ml. of 30% hydrogen peroxide was heated at 70–80° for 48 hours and the reaction mixture then was evaporated to dryness under reduced pressure. The brown residue was recrystallized from water using charcoal and then was sublimed at 135–145°/0.5 mm. to remove unreacted starting material. The residue from the sublimation (m.p. 194°) was recrystallized from water with the use of charcoal and the resulting silken needles were sublimed to give 2-hydroxynicotinic acid, m.p. 258–260°.

Nicotinic acid-1-oxide (VII). This material was prepared essentially according to the procedure of Clemo (17) in yields of 70–80%; m.p. 254–255° (dec.).

2-Chloronicotinamide (III). *Method A.* A mixture of 1.0 g. of 2-chloronicotinonitrile, 0.4 g. of solid potassium hydroxide, and 20 ml. of absolute ethanol was treated with hydrogen peroxide as described above under the synthesis of VI. Concentration of the reaction mixture and cooling gave 0.67 g. of pure 2-chloronicotinamide, m.p. 163–165°. Further concentration of the filtrate yielded 0.07 g. of a solid which was washed with dilute sodium carbonate solution followed by water to give an additional 0.03 g. of 2-chloronicotinamide; total yield, 0.70 g. (62%).

Anal. Calc'd for $C_6H_5ClN_2O$: C, 46.0; H, 3.2; N, 17.9.

Found: C, 46.3; H, 3.2; N, 17.6.

Method B. A mixture of 7.0 g. (0.05 mole) of nicotinic acid-1-oxide (VII), 21.2 g. (0.10 mole) of phosphorus pentachloride, and 23 ml. of phosphorus oxychloride was heated at 115–120° for 1½ hours. The excess phosphorus oxychloride then was removed by evaporation under reduced pressure and to the residual syrup was added 100 ml. of hot benzene saturated with anhydrous ammonia. The benzene solution was then cooled to 0–5° and anhydrous ammonia was passed through the mixture for ten minutes. Evaporation of the benzene solution to dryness and extraction of the resulting orange residue with chloroform in a Soxhlet apparatus for 24 hours gave a yellow extract which was evaporated to dryness. The yellow residual solid gave 2.8 g. (35%) of 2-chloronicotinamide upon recrystallization

from alcohol. Final purification was effected by sublimation at 145°/0.5 mm., and the product (m.p. 164–165°) was identical with that prepared by Method *A* above.

2-Aminonicotinic acid (IV). *Method A.* A solution of 1.0 g. of 2-aminonicotinonitrile (V) in 5 ml. of concentrated hydrochloric acid was heated in a sealed tube for five hours at 165°. The reaction mixture solidified to a white crystalline mass upon cooling. The solid mass was dissolved in 20 ml. of water, and the solution was evaporated to 10 ml. and concentrated ammonium hydroxide was added to *p*H 5. Chilling followed by filtration gave 1.1 g. (94.5%) of colorless 2-aminonicotinic acid, m.p. 306–307° (dec.), which was identical with an authentic sample of 2-aminonicotinic acid prepared from quinolinic acid (22).

Method B. A mixture of 2.0 g. of 2-chloronicotinic acid (VIII) and 50 ml. of concentrated ammonium hydroxide was placed in a glass liner within a stainless-steel bomb and heated at 175° for 3½ hours. Evaporation of the reaction mixture gave 0.50 g. of crude 2-aminonicotinic acid, m.p. 285° (dec.), which then was recrystallized from water (charcoal) to give 0.3 g. (17%) of 2-aminonicotinic acid, m.p. 306° (dec.).

Method C. A mixture of 3.3 g. of 2-chloronicotinamide (III), 50 ml. of concentrated ammonium hydroxide, and 0.3 g. of sodium iodide was heated as described above at 155° for five hours. After evaporation of the reaction mixture to dryness, the residue was washed with ice-water and then recrystallized from water (charcoal) to give 0.4 g. (14%) of 2-aminonicotinic acid, m.p. 306° (dec.).

Method D. A mixture of 3.3 g. of 2-chloronicotinonitrile (II) and 50 ml. of concentrated ammonium hydroxide was heated as described above at 155° for six hours to give 0.7 g. (21%) of 2-aminonicotinic acid, m.p. 307° (dec.).

2-Chloronicotinic acid (VIII). A mixture of 14 g. (0.10 mole) of nicotinic acid-1-oxide, 42.4 g. (0.20 mole) of phosphorus pentachloride, and 40 ml. of phosphorus oxychloride was heated at 115–120° for 1½ hours. After removing the excess phosphorus oxychloride by distillation under reduced pressure, the residual syrup was poured over ice (*ca.* 100 g.) and the mixture was allowed to stand at 0° overnight. The solid which was separated by filtration was recrystallized from water using s small amount of charcoal to give 6.6 g. (41%) of colorless 2-chloronicotinic acid, m.p. 192–193° (dec.). The analytical sample was prepared by sublimation at 145–150°/0.5 mm.

Anal. Calc'd for $C_6H_4ClNO_2$: C, 45.7; H, 2.6; N, 8.9.
Found: C, 46.0; H, 2.6; N, 8.9.

4-Chloronicotinic acid (IX). Evaporation of the remaining filtrates above to about 50 ml. gave 0.8 g. (5%) of 4-chloronicotinic acid, which was purified by sublimation at 135–140°/0.5 mm., m.p. 164°.

Anal. Calc'd for $C_6H_4ClNO_2$: C, 45.7; H, 2.6; N, 8.9.
Found: C, 45.4; H, 2.6; N, 8.6.

4-Aminonicotinic acid (X). A mixture of 0.4 g. of 4-chloronicotinic acid and 25 ml. of concentrated ammonium hydroxide was placed in a glass liner within a stainless-steel bomb and heated at 175° for 5½ hours. Evaporation of the reaction mixture and crystallization of the residue from water gave 4-aminonicotinic acid, m.p. 328° (dec.).

4-Nitro-3-picoline-1-oxide (XIII). The preparation of this compound from XII has been briefly mentioned in the literature (25), but no details were given, and the properties of XIII were not described. Our preparation of XIII has therefore been reported in detail.

To a cooled (0–5°) mixture of 27.5 ml. of nitric acid (*d.* 1.50) and 35 ml. of sulfuric acid (*d.* 1.84) was added slowly 10 g. of 3-picoline-1-oxide (24). The reaction mixture then was heated slowly to 100–105° and held there for two hours. The cooled mixture was added to ice and sodium carbonate was added to *p*H 2–3. At this point heavy crystallization of 4-nitro-3-picoline-1-oxide and sodium sulfate occurred. After allowing the mixture to stand overnight, the yellow solid was separated by filtration and washed well with ice-water; yield 7.7 g., m.p. 136–137°. The combined filtrates were extracted with hot chloroform, and the extracts were dried over sodium sulfate and evaporated to dryness. Recrystallization of the residue from acetone gave an additional 2.9 g. of 4-nitro-3-picoline-1-oxide, m.p. 136–137° (total yield, 10.7 g. (76%)). The product was very soluble in hot acetone and

chloroform and slightly soluble in water and alcohol. The analytical sample was prepared by sublimation at 115–120°/0.5 mm., m.p. 136–137°.

Anal. Calc'd for $C_6H_6N_2O_3$: C, 46.8; H, 3.9; N, 18.2.

Found: C, 47.0; H, 3.9; N, 17.9.

4-Amino-3-picoline (XV). The following reduction procedure is adapted from similar procedures described by Hertog (3, 5, 6, 9). A mixture of 10 g. of 4-nitro-3-picoline-1-oxide, 300 ml. of glacial acetic acid, and 30 g. of iron powder was heated at 100° with stirring for two hours. The cooled reaction mixture was diluted with water, adjusted to *p*H 10–11 with sodium hydroxide, 200 ml. of ether was added, and the precipitated iron hydroxide was filtered with suction, care being taken that the iron hydroxide was continually covered with a layer of ether during the filtration. The collected solid was extracted several times with ether, the aqueous filtrate was extracted with ether, and the combined ether extracts were dried over sodium sulfate and evaporated to dryness. The residual solid was recrystallized from high-boiling petroleum ether to give 4.4 g. (63%) of 4-amino-3-picoline, m.p. 108–109°; *picrate*, m.p. 224–225° (28).

4-Aminonicotinic acid (X). A mixture of 2.5 g. of 4-amino-3-picoline and 6 ml. of acetic anhydride was heated under reflux for 15 minutes, cooled, and the excess acetic anhydride was distilled under reduced pressure. The residual oil was taken up in hot benzene and the benzene solution was boiled with charcoal for 20 minutes and filtered. The charcoal was extracted with an additional quantity of hot benzene and the combined benzene solutions were concentrated to a small volume and chilled to give 1.51 g. (43%) of 4-acetamido-3-picoline, m.p. 148–153° (28). This material was dissolved in 200 ml. of water (70°) and 3.8 g. of potassium permanganate was added in one portion with vigorous mechanical stirring. Stirring and heating (70–75°) were maintained for a period of six hours. After addition of Filter Cel, the solution was filtered and the collected manganese dioxide was extracted several times with boiling water. The combined filtrates were evaporated to dryness, the residual solid was dissolved in 10 ml. of water, and the solution was acidified to *p*H 3 with concentrated hydrochloric acid. After boiling for 20 minutes, the solution was readjusted to *p*H 5 with concentrated ammonium hydroxide, whereupon 4-aminonicotinic acid precipitated. The solution was cooled at 0° overnight and the product was collected by filtration, washed with ice-water, and dried at 110°; yield, 0.7 g. (50.5% based on 4-acetamido-3-picoline), m.p. 328° (dec.) (28).

SUMMARY

Convenient syntheses of 2-chloronicotinonitrile (II), 2-chloronicotinamide (III), 2-aminonicotinonitrile (V), 2-aminonicotinamide (VI), 2-hydroxynicotinic acid (XI), 2-chloronicotinic acid (VIII), 2-aminonicotinic acid (IV), and 4-aminonicotinic acid (X) from nicotinamide-1-oxide (I), nicotinic acid-1-oxide (VII), and 3-picoline-1-oxide (XII) are described.

URBANA, ILLINOIS

REFERENCES

(1) MEISENHEIMER, *Ber.*, **59**, 1848 (1926).
(2) A review of recent Japanese work in this field has been given by OCHIAI, *J. Org. Chem.*, **18**, 534 (1953).
(3) DEN HERTOG AND OVERHOFF, *Rec. trav. chim.*, **69**, 468 (1950).
(4) DEN HERTOG AND BOELRIJK, *Rec. trav. chim.*, **70**, 578 (1951).
(5) DEN HERTOG AND COMBÉ, *Rec. trav. chim.*, **70**, 581 (1951).
(6) DEN HERTOG, KOLDER, AND COMBÉ, *Rec. trav. chim.*, **70**, 591 (1951).
(7) DEN HERTOG AND COMBÉ, *Rec. trav. chim.*, **71**, 745 (1952).
(8) DEN HERTOG, HENKENS, AND VAN ROON, *Rec. trav. chim.*, **71**, 1145 (1952).
(9) DEN HERTOG, HENKENS, AND DILZ, *Rec. trav. chim.*, **72**, 296 (1953).

(10) JUJO, *J. Pharm. Soc. Japan*, **66**, 21 (1946); *Chem. Abstr.*, **45**, 6200i (1951).
(11) SHIMIZU, NAITO, OHTA, YOSHIKAWA, AND DOHMORI, *J. Pharm. Soc. Japan*, **72**, 1474 (1952); *Chem. Abstr.*, **47**, 8077h (1953).
(12) SPÄTH AND KOLLER, *Ber.* **56**, 887 (1923).
(13) VON SCHICK, BINZ, AND SCHULZ, *Ber.*, **69**, 2600 (1936).
(14) CALDWELL, TYSON, AND LAUER, *J. Am. Chem. Soc.*, **66**, 1484 (1944).
(15) DORNOW AND PETERLEIN, *Ber.*, **82**, 259 (1949).
(16) KIRPAL, *Monatsh.*, **21**, 962 (1900).
(17) CLEMO AND KOENIG, *J. Chem. Soc.*, S231 (1949).
(18) DAL MONTE CASONI, *Bull. sci. facolta chim. ind. Bologna*, **8**, 137 (1950), *Chem. Abstr.*, **45**, 8013a (1951).
(19) SEIDE, *Ber.*, **57**, 1802 (1924.)
(20) FIBEL AND SPOERRI, *J. Am. Chem. Soc.*, **70**, 3908 (1948).
(21) PHILIPS, *Ann.*, **288**, 253 (1895).
(22) MANN AND REID, *J. Chem. Soc.*, 2057 (1952).
(23) SUCHARDA, *Ber.*, **58**, 1728 (1925).
(24) BOEKELHEIDE AND LINN, *J. Am. Chem. Soc.*, **76**, 1286 (1954).
(25) TALIKOWA, *Wiadomości Chemi.*, **7**, 169 (1953).
(26) GOLDSCHMIEDT AND STRACHE, *Monatsh.*, **10**, 156 (1889).
(27) KIRPAL, *Monatsh.*, **23**, 243 (1902).
(28) CLEMO AND SWAN, *J. Chem. Soc.*, 198 (1948).